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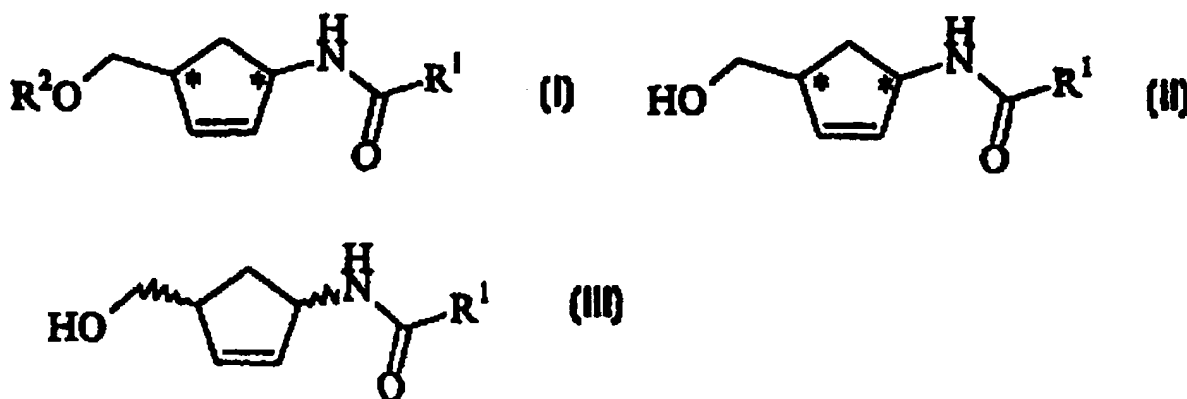
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(71) Demandeur/Applicant:
LONZA AG, CH
(72) Inventeurs/Inventors:
PETERSEN, MICHAEL, CH;
ETTER, KAY-SARA, CH;
BRIEDEN, WALTER, CH
(74) Agent: G. RONALD BELL & ASSOCIATES

(54) Titre : PROCÉDE DE PRODUCTION DE DERIVES 1-AMINO-4-(HYDROXYMETHYL)-CYCLOPENT-2-ENE
OPTIQUEMENT ACTIFS

(54) Title: PROCESS FOR PREPARING OPTICALLY ACTIVE 1-AMINO-4-(HYDROXYMETHYL) CYCLOPENT-2-ENE
DERIVATIVES



(57) Abrégé/Abstract:

The invention relates to a new method for producing enantiomer-enriched 1-amino-4-(hydroxymethyl)-cyclopent-2-ene derivatives of the general formulae (I) and (II) in which R¹ is hydrogen or a possibly substituted C₁₋₈ alkyl rest, aryl rest or cycloalkyl rest and R² is a possibly substituted acyl. According to said method a racemic 1-amino-4-(hydroxymethyl)-cyclopent-2-ene derivative of general formula (III), in which R¹ has the meaning given above, is converted using a hydrolase and in the presence of an acylation agent.

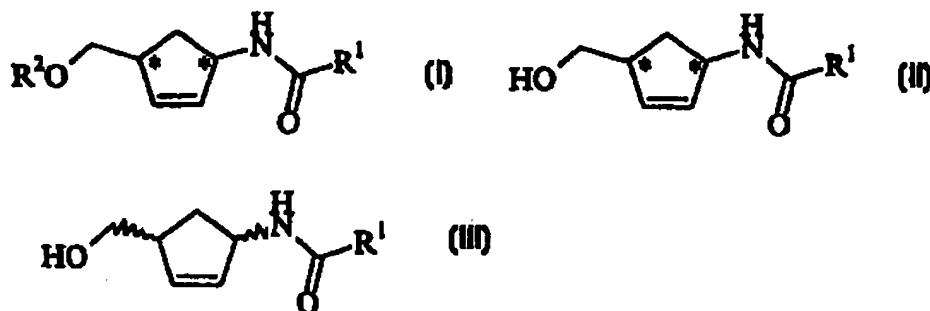


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(54) Title: METHOD FOR PRODUCING OPTICALLY ACTIVE 1-AMINO-4-(HYDROXYMETHYL)-CYCLOPENT-2-ENE DERIVATIVES

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON OPTISCH AKTIVEN 1- AMINO-4- (HYDROXYMETHYL)- CYCLOPENT-2- EN-DERIVATEN



(57) Abstract

The invention relates to a new method for producing enantiomer-enriched 1-amino-4-(hydroxymethyl)-cyclopent-2-ene derivatives of the general formulae (I) and (II) in which R¹ is hydrogen or a possibly substituted C₁₋₈ alkyl rest, aryl rest or cycloalkyl rest and R² is a possibly substituted acyl. According to said method a racemic 1-amino-4-(hydroxymethyl)-cyclopent-2-ene derivative of general formula (III), in which R¹ has the meaning given above, is converted using a hydrolase and in the presence of an acylation agent.

(57) Zusammenfassung

Beschrieben wird ein neues Verfahren zur Herstellung von enantiomerenangereicherten 1- Amino-4-(hydroxymethyl)-cyclopent-2-en-Derivaten der allgemeinen Formeln (I), (II), worin R¹ Wasserstoff oder einen gegebenenfalls substituierten C₁₋₈- Alkylrest, Arylrest oder Cycloalkylrest bedeutet und R² gegebenenfalls substituiertes Acyl bedeutet, umfassend die Umsetzung eines racemischen 1-Amino-4-(hydroxymethyl)-cyclopent- 2-en-Derivats der allgemeinen Formel (III), worin R¹ die genannte Bedeutung hat, mittels einer Hydrolase in Gegenwart eines Acylierungsmittels.

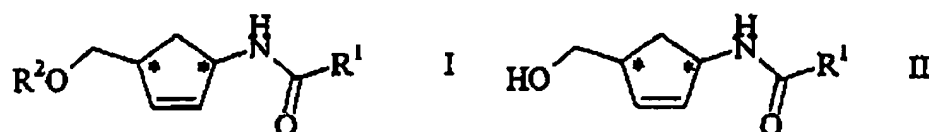
Process for preparing optically active 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivatives

Description

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The present invention relates to a novel process for preparing enantiomerically enriched 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivatives of the general formulae

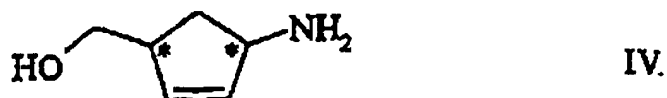
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in which R¹ is hydrogen, alkyl, aryl or cycloalkyl and R² is acyl, and in particular to reacting them further to give the corresponding enantiomerically enriched 1-amino-4-(hydroxymethyl)cyclopent-2-ene compounds of the formula IV

20



25

Enantiomerically enriched 1-amino-4-(hydroxymethyl)cyclopent-2-ene of the formula IV, such as, for example, (1R,4S)-1-amino-4-(hydroxymethyl)cyclopent-2-ene, is an important intermediate in the preparation of carbocyclic nucleosides, such as, for example, carbovir (Campbell et al., J. Org. Chem. 1995, 60, 4602-4616).

30

Hereinbelow, "enantiomerically enriched" compounds are understood as compounds having an enantiomeric excess (ee) of more than 20 %.

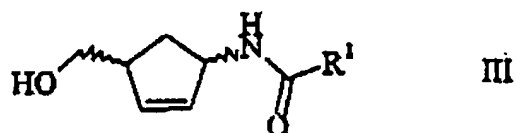
A number of processes for preparing (1R,4S)-1-amino-4-(hydroxymethyl)cyclopent-2-ene have been known up until now. WO 97/45529, for example, describes a biotechnological process for preparing (1R,4S)-1-amino-

4-(hydroxymethyl)cyclopent-2-ene starting from racemic
 cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene
 using microorganisms which employ the latter as the
 only carbon source, as the only nitrogen source or as
 5 the only carbon and nitrogen source. This process has
 the disadvantage that it has to be carried out in a
 fermenter.

It was the object of the present invention to
 provide an alternative, simple and cost-efficient
 10 process for preparing enantiomerically enriched
 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivatives of
 the formula I and II and enantiomerically enriched
 1-amino-4-(hydroxymethyl)cyclopent-2-ene compounds of
 the formula IV.

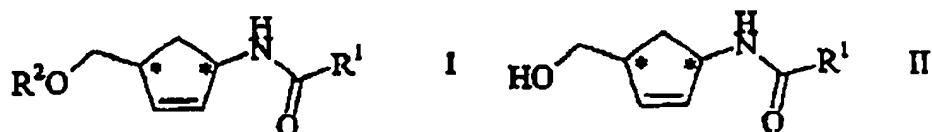
15 This object is achieved by the processes
 according to Claims 1, 5 and 7.

According to the invention, the object is
 achieved, in accordance with Claim 1, by converting a
 racemic 1-amino-4-(hydroxymethyl)cyclopent-2-ene
 20 derivative of the general formula



in which R¹ is hydrogen, an optionally substituted,
 25 linear or branched C₁₋₈-alkyl radical, aryl radical or
 cycloalkyl radical using a hydrolase in the presence of
 an acylating agent into the enantiomerically enriched
 1-amino-4-(hydroxymethyl)-cyclopent-2-ene derivatives
 of the general formulae

30



in which R¹ is as defined above and R² is optionally
 substituted acyl.

The starting materials, the racemic 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivatives of the general formula III, can be prepared starting from (\pm)-2-azabicyclo[2.2.1]hept-5-ene-3-one, in accordance with
5 WO 97/45529. Preference is given to using the cis-racemic starting materials.

The term alkyl, as used in this context, includes both linear and branched alkyl. Alkyl can be substituted or unsubstituted. C₁₋₈-alkyl is in
10 particular methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl and its isomers, hexyl and its isomers, heptyl and its isomers or octyl and its isomers. Substituted C₁₋₈-alkyl is understood as C₁₋₈-alkyl which is substituted by one or more halogen
15 atoms, by OR³ or by NR³R⁴, R³ and R⁴ being identical or different and being hydrogen or branched or linear C₁₋₈-alkyl, aryl or cycloalkyl. The halogen atom used may be F, Cl, Br or I. Examples of NR³R⁴s are methylamino, N-methyl-N-ethylamino, 1-piperidinyl or aminomethyl.
20 Examples of OR³s are methoxy, methoxymethyl, ethoxy, propoxy and phenoxy.

Aryl is preferably understood as benzyl or phenyl, substituted or unsubstituted. Substituted aryl is understood hereinbelow as aryl which is substituted
25 by one or more halogen atoms C₁₋₄-alkyl groups, C₁₋₄-alkoxy groups, amino, cyano or nitro groups. The substituted benzyl used is preferably chloro- or bromobenzyl, and the substituted phenyl used is preferably bromo- or chlorophenyl.

Cycloalkyl is advantageously substituted or
30 unsubstituted C₃₋₇-cycloalkyl, for example cyclopropyl, cyclopentyl or cyclohexyl. Examples of suitable substituents are those mentioned for aryl.

Acyl corresponds to the acid component of the
35 acylating agent used.

Acyl is preferably C₁₋₆-alkanoyl, unsubstituted or substituted by one or more halogen atoms, C₁₋₄-alkoxy, aryl, hydroxy, amino, cyano, nitro, and/or COOR, where R is C₁₋₄-alkyl. Examples of unsubstituted

or substituted acyl radicals are acetyl, propionyl, butyryl, chloroacetyl, bromoacetyl, dichloroacetyl, cyanoacetyl, methoxycarbonyl, ethoxycarbonyl, methoxyethanoyl, hydroxybutyryl, hydroxyhexanoyl, 5 phenylcarbonyl, chlorophenylcarbonyl and benzylcarbonyl.

Suitable acylating agents are, in general, carboxylic acid derivatives, such as carboxamides, carboxylic anhydrides or carboxylic esters.

10 The carboxylic esters used may be alkoxycarboxylic esters, such as ethyl methoxyacetate, or propyl methoxyacetate, C₁₋₆-carboxylic esters, such as butyl acetate, ethyl butyrate, phenyl butyrate, trichloroethyl butyrate, ethyl hexanoate, vinyl 15 butyrate, glycerol esters, such as tributyrin (glyceryl tributyrate), glycol esters, such as glycol dibutyrate, diethyl diglycolate, or dicarboxylic esters, such as vinyl succinate, cyano-substituted esters, such as cyanoacetic esters, or cyclic carboxylic esters, such as 20 as butyrolactone, caprolactone.

The carboxamides used may be the amides which correspond to the abovementioned esters.

The carboxylic anhydrides used may be simple, mixed or cyclic anhydrides, such as butyric anhydride, 25 acetyl benzoate, succinic anhydride.

The hydrolases used may be lipases, esterases or proteases. Suitable for use as lipase are customary lipases, such as, for example, Novo-Lipase SP523 from *Aspergillus oryzae* (Novozym 398), Novo-Lipase SP524 30 from *Aspergillus oryzae* (Lipase = Palatase 20000L from Novo), Novo-Lipase SP525 from *Candida antarctica* (Lipase B Novozym 435, immobilized), Novo-Lipase SP526 from *Candida antarctica* (Lipase A = Novozym 735, immobilized), Lipase kits from Fluka (1 & 2), Amano P 35 Lipase, lipase from *Pseudomonas* sp., lipase from *Candida cylindracea*, lipase from *Candida lipolytica*, lipase from *Mucor miehei*, lipase M from *Mucor javanicus* (Amano), lipase from *Aspergillus niger*, lipase from *Bacillus thermocatenuatus*, lipase from *Candida*

antarctica, Lipase AH (Amano; immobilized), Lipase P (Nagase), Lipase AY from *Candida rugosa*, Lipase G (Amano 50), Lipase F (Amano F-AP15), Lipase PS (Amano), Lipase AH (Amano), Lipase D (Amano), Lipase AK from
5 *Pseudomonas fluorescens*, Lipase PS from *Pseudomonas cepacia*, Newlase I from *Rhizopus niveus*, Lipase PS-CI (immobilized lipase from *Pseudomonas cepacia*).

These lipases can be used, as is known to the person skilled in the art, as cell-free enzyme extracts
10 or else in the corresponding microorganism cell.

Suitable proteases are likewise commercially available proteases, for example serine proteases such as subtilisin. The subtilisin used may be, for example, savinase from *Bacillus* sp., alcalase, subtilisin from
15 *Bacillus licheniformis* and proteases from *Aspergillus*, *Rhizopus*, *Streptomyces* or *Bacillus* sp.

Depending on which hydrolase is selected, one of the two enantiomers of a racemic, for example cis-racemic, 1-amino-4-(hydroxymethyl)cyclopent-2-ene of
20 the formula III is acylated (compounds of the formula I), whereas the other enantiomer remains unchanged (compounds of the formula II). The two enantiomers can then be separated.

Different hydrolases may have different
25 stereospecificities. If, for example, cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene is reacted with lipase M and an acylating agent, the (1R, 4S)-enantiomer is acylated specifically and can be separated from the non-acylated (1S, 4R)-enantiomer. If
30 the hydrolase used is, for example, Savinase (protease from *Bacillus* sp.), the (1S, 4R)-enantiomer is acylated specifically, whereas the (1R, 4S)-enantiomer remains.

The hydrolase-catalyzed acylation is advantageously carried out at a temperature of from 0
35 to 70°C, preferably at a temperature of from 15 to 45°C.

The hydrolase-catalyzed acylation can be carried out in a protic or aprotic organic solvent. Suitable aprotic organic solvents are ethers, aliphatic

hydrocarbons, organic bases and carboxylic acid derivatives. Ethers which may be used are tert-butyl methyl ether, diisopropyl ether, dibutyl ether, dioxane or tetrahydrofuran. Suitable aliphatic hydrocarbons are
5 hexane, heptane, octane. Suitable organic bases are pyridines or trialkylamines, such as triethylamine. Possible carboxylic acid derivatives are, for example, ethyl acetate or the above-described acylating agents.

The enantiomerically enriched 1-amino-4-
10 (hydroxymethyl)cyclopent-2-ene derivatives of the general formula I or II formed in the hydrolase-catalyzed acylation can, after separation, be directly chemically hydrolyzed into the corresponding enantiomerically enriched 1-amino-4-(hydroxymethyl)-
15 cyclopent-2-ene isomers of the formula IV



IV.

Alternatively, the enantiomerically enriched
20 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivative of the general formula I which has been separated off can initially, by choosing the appropriate hydrolysis conditions, be hydrolysed step-wise back to the corresponding enantiomerically enriched 1-amino-4-
25 (hydroxymethyl)cyclopent-2-ene derivative of the general formula II which, if desired, is then converted by further chemical hydrolysis as above into the corresponding enantiomerically enriched 1-amino-4-(hydroxymethyl)cyclopent-2-ene of the formula IV.

30 Advantageously, the chemical hydrolysis is carried out using an alkali metal hydroxide or ammonia. The alkali metal hydroxide used may be sodium hydroxide or potassium hydroxide.

The chemical hydrolysis can be carried out at a
35 temperature of from 20 to 100°C, preferably at a temperature of from 60 to 80°C.

The preferred enantiomerically enriched 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivative of

the general formula I is the (1R,4S)- and (1S,4R)-N-acetyl-1-amino-4-(propylcarbonyloxymethyl)cyclopent-2-ene ($R^1 = CH_3$, $R^2 = \text{propylcarbonyl}$), and the preferred 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivatives of
5 the general formula II are the (1R,4S)- and (1S,4R)-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene, which are then chemically hydrolyzed preferably into the (1R,4S)- or (1S,4R)-1-amino-4-(hydroxymethyl)cyclopent-2-ene.

Examples

Example 1

50 mg of cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene and 250 µl of vinyl butyrate were dissolved in 5 ml of 2-methyl-2-butanol. 300 mg of Lipase M (from *Mucor javanicus*; Amano) were added, and the suspension was stirred at room temperature. After 16 h, (1S,4R)-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene was present in an enantiomeric excess of 98.5 % (GC).

After separating (1S,4R)-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene and the (1R,4S)-N-acetyl-1-amino-4-(propylcarbonyloxymethyl)cyclopent-2-ene formed (chromatography over silica gel 60), the two compounds were separately taken up in 2M aqueous sodium hydroxide solution. (1S, 4R)-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene was converted by stirring at 80°C (70 h), into the enantiomerically pure or enantiomerically enriched cis-1-amino-4-(hydroxymethyl)cyclopent-2-ene while (1R, 4S)-N-acetyl-1-amino-4-(propylcarbonyloxymethyl)cyclopent-2-ene was converted by stirring at room temperature (5 h) into the enantiomerically pure or enantiomerically enriched cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene.

Example 2

10 mg of cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene and 50 µl of vinyl butyrate were dissolved in 1 ml of dioxane. 30 mg of Lipase M (from *Mucor javanicus*; Amano) were added, and the suspension was stirred at room temperature. After 20 h, (1S,4R)-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene was present in an enantiomeric excess of 91.0 % (GC).

Example 3

10 mg of cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene and 50 µl of vinyl butyrate were dissolved in 1 ml of 2-methyl-2-butanol. 40 mg of

savinase (protease from *Bacillus* sp.; Novo Nordisk) were added, and the suspension was stirred at room temperature. After 20 h, (1R,4S)-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene was present in an enantiomeric excess of 91.7 % (GC).

Example 4

10 mg of cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene and 50 µl of vinyl butyrate were dissolved in 1 ml of dioxane. 40 mg of savinase (protease from *Bacillus* sp.; Novo Nordisk) were added, and the suspension was stirred at room temperature. After 200 h, (1R,4S)-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene was present in an enantiomeric excess of 81.7 % (GC).

Example 5

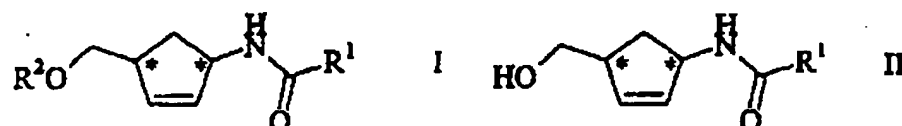
100 mg of cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene and 0.5 mmol of vinyl butyrate were dissolved in 1 ml of 2-methyl-2-butanol. 20 mg of Lipase PS (from *Pseudomonas cepacia*) were added, and the suspension was stirred at room temperature. After 21 h, (1R,4S)-N-acetyl-1-amino-4-(hydroxymethyl)-cyclopent-2-ene is present in an enantiomeric excess of 44 % (GC).

Example 6

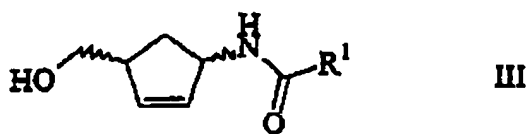
10 mg of cis-N-acetyl-1-amino-4-(hydroxymethyl)cyclopent-2-ene and 0.03 mmol of tributyrin were dissolved in 1 ml of 2-methyl-2-butanol. 20 mg of Lipase PS (*Pseudomonas cepacia*) were added, and the suspension was stirred at room temperature. After 200 h, (1R,4S)-N-acetyl-1-amino-4-(hydroxymethyl)-cyclopent-2-ene is present in an enantiomeric excess of 32 % (GC).

Patent Claims

1. Process for preparing enantiomerically enriched
1-amino-4-(hydroxymethyl)cyclopent-2-ene derivatives of
5 the general formulae



- in which R¹ is hydrogen or an optionally substituted
10 C₁₋₈-alkyl radical, aryl radical or cycloalkyl radical
and R² is an optionally substituted acyl, in that a
racemic 1-amino-4-(hydroxymethyl)cyclopent-2-ene deriv-
ative of the general formula



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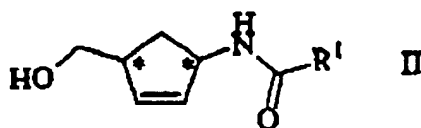
in which R¹ is as defined above is reacted using a
hydrolase in the presence of an acylating agent.

2. Process according to Claim 1, characterized in
20 that the hydrolase used is a protease, esterase or
lipase.

3. Process according to Claim 1 or 2,
characterized in that the hydrolase-catalyzed acylation
is carried out at a temperature of from 0 to 70°C.

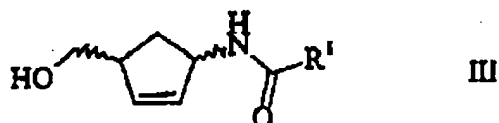
- 25 4. Process according to one of Claims 1 to 3,
characterized in that the hydrolase-catalyzed acylation
is carried out in a protic or aprotic organic solvent.

5. Process for preparing enantiomerically enriched
1-amino-4-(hydroxymethyl)cyclopent-2-ene derivatives of
30 the general formula



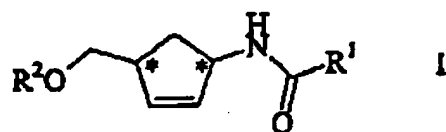
characterized in that a racemic 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivative of the general formula

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in which R¹ is as defined in Claim 1 is converted using a hydrolase in the presence of an acylating agent into enantiomerically enriched 1-amino-4-(hydroxymethyl)-cyclopent-2-ene derivatives of the general formula I

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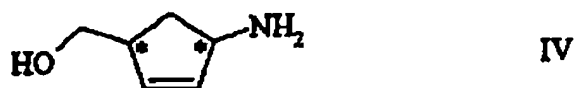


15 in which R¹ and R² are as defined in Claim 1, and these are then chemically hydrolyzed into the corresponding enantiomers of the general formula II.

6. Process according to Claim 5, characterized in that the chemical hydrolysis is carried out at a temperature of from 20 to 100°C.

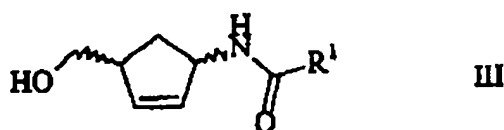
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7. Process for preparing enantiomerically enriched 1-amino-4-(hydroxymethyl)cyclopent-2-ene of the formula



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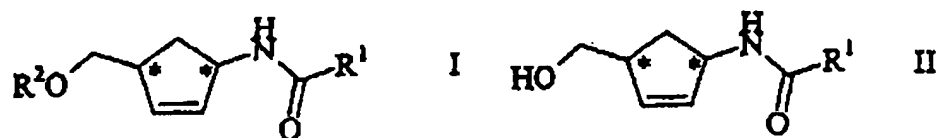
characterized in that a racemic 1-amino-4-(hydroxymethyl)cyclopent-2-ene derivative of the general formula



30

in which R¹ is as defined in Claim 1 is converted using a hydrolase in the presence of an acylating agent into

enantiomerically enriched 1-amino-4-(hydroxymethyl)-cyclopent-2-ene derivatives of the general formula



5

in which R^1 and R^2 are as defined in Claim 1, and these are then chemically hydrolyzed into the corresponding enantiomerically enriched 1-amino-4-(hydroxymethyl)-cyclopent-2-ene isomers of the formula IV.

